Patisiran for treating hereditary transthyretin-related amyloidosis: A Highly Specialised Technology Appraisal

Addendum - ERG critique of the company's updated model

Paul Tappenden

Aline Navega Biz

John W Stevens

School of Health and Related Research (ScHARR)

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1. Introduction

The current NICE Evaluation Consultation Document[1] (ECD) for patisiran makes the following recommendation:

"Patisiran is not recommended, within its marketing authorisation, for treating hereditary transthyretin-related amyloidosis in adults" (NICE ECD,[1] December 2018).

Following the second NICE Appraisal Committee meeting on 12th February 2019, NICE asked the company to consider the following amendments to their health economic analysis:

- Consider revising the simple PAS and move away from commercial arrangements
- Consider approaches to introduce the impact of autonomic neuropathy symptoms, highlighted by patients and clinicians as being of particular importance
- Consider a stopping rule in accordance with the marketing authorisation: Patisiran to be stopped if patients enter FAP stage 3 (PND IV)
- Consider adding caregiver disutilities to achieve consistency with the inotersen model. The committee accepted the inotersen model which assumes 1 full-time caregiver for each patient in the first 2 stages of the disease and 2 carers at stage 3.

In April 2019, the company submitted an additional evidence submission[2] containing new analyses undertaken using an updated version of the company's model. The executable model was provided for scrutiny by the ERG.

The company's new analyses based on the updated model include the following:

[redacted]

(b) An assumption that mortality risk does not increase with increasing PND score
(c) Additional disutilities applied to the BSC group which are intended to reflect the additional impact of GI-related autonomic dysfunction
(d) A stopping rule in which patients discontinue patisiran on progression to PND IV and the re-introduction of the log normal time-to-treatment discontinuation function applied to all other model health states
(e) The inclusion of caregiver disutilities based on the inotersen model.

This addendum provides a summary and critique of the company's new analyses. Section 3 presents further analyses undertaken by the ERG using the company's updated model.

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Following further communication between the company, NICE and the ERG, the company submitted an amended version of the updated model; all results presented in this addendum are based on this amended version of the updated model.

2.1 [redacted]

2.2 Exclusion of PND-related mortality risks

The company's updated model makes the assumption that mortality risk for patients with hATTR amyloidosis does not increase with increasing PND score. Hence, within the company's new analyses, the hazard ratios (HRs) for mortality for all PND states are set equal to 2.01 (the HR used by the company to characterise mortality risk in patients with hATTR amyloidosis relative to mortality in the general population), unless the patient has an NT-proBNP level ≥3,000pg/mL. The company's additional evidence submission states that this assumption has been made because *"As documented in the extensive natural history of disease in the UK and the attestation of clinical experts, the leading cause of death of hATTR amyloidosis in the country is cardiomyopathy"* (Company's additional evidence submission,[2] April 2019). The company's additional evidence submission also highlights that the ERG report criticised the source of PND-related mortality (Suhr *et al*[3]) and the complexity of the method used by the company to derive mortality risks conditional on the model health states. The company also notes that the ERG's exploratory analyses included a scenario in which PND-related mortality was removed from the model.

As described in the original ERG report, the HRs are "chained" together – for example, the HR for mortality in state PND IIIa and NT-proBNP≥3,000pg/mL is calculated as the product of: (i) the HR for hATTR amyloidosis versus general population mortality; (ii) the HR for PND IIIa/b versus PND 0-II and (iii) the HR for NT-proBNP≥3,000pg/mL versus NT-proBNP<3,000pg/mL. These HRs are assumed to be constant over time. Table 1 presents the HRs for death according to PND score and NT-proBNP level applied in the company's original model alongside those applied in the company's updated model. Figure 1 presents the modelled survival trajectories for the patisiran and BSC groups

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including both PND and NT-proBNP risks (as per the company's original model), and including NT-proBNP risks only (as per the company's updated model). Table 2 shows the impact of re-introducing the PND-related HRs for death on the results of the company's updated model (in line with the company's original model).

Table 1: HRs for death applied in company's original model and company's updated model

Health state(s)	Mortality HR applied in health state	
	Company's original model (PND and NT-proBNP mortality risks)*	Company's updated model (NT-proBNP risks only)
PND 0-II, NT-proBNP<3,000pg/mL	2.01	2.01
PND IIIa and IIIb, NT-proBNP<3,000pg/mL	2.62	2.01
PND IV, NT-proBNP<3,000pg/mL	9.53	2.01
PND 0-II, NT-proBNP≥3,000pg/mL	4.12	4.12
PND IIIa and IIIb, NT-proBNP≥3,000pg/mL	5.35	4.12
PND IV, NT-proBNP≥3,000pg/mL	19.49	4.12

Figure 1: Company's new and original mortality projections

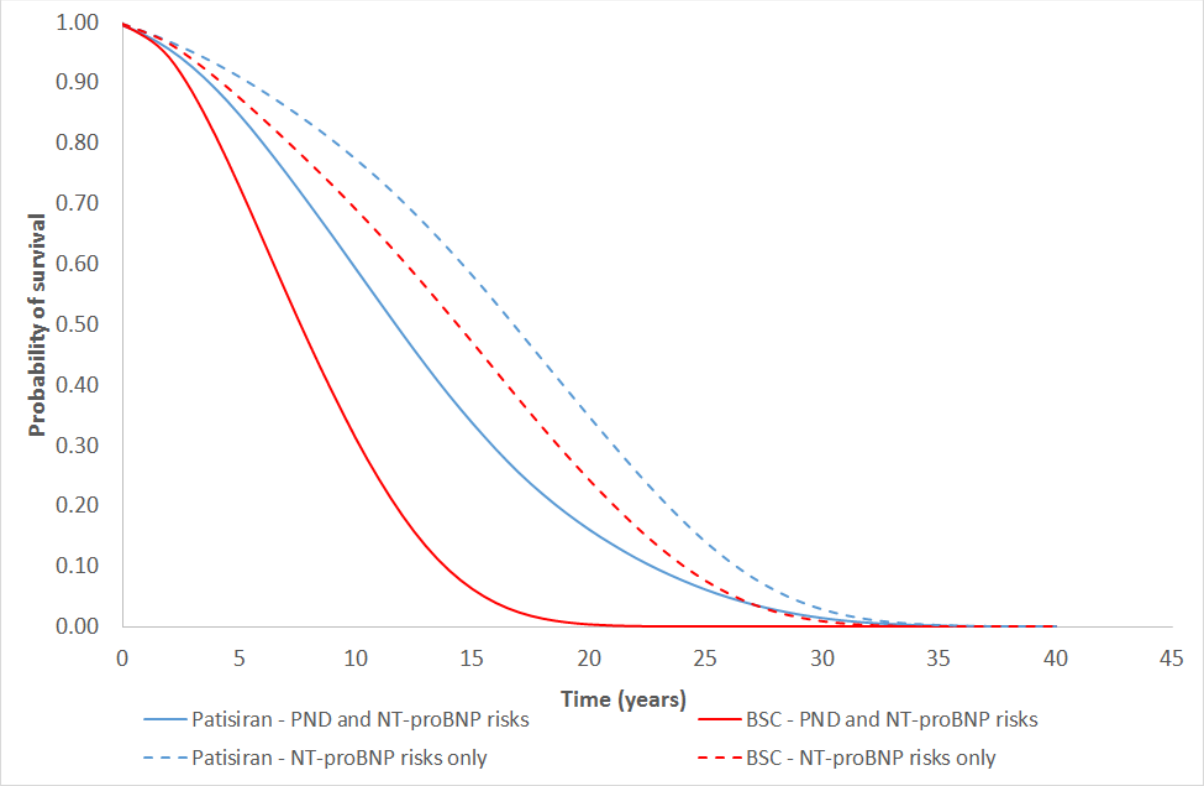

Table 2: Company's updated model results – with/without PND-related mortality HRs

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Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – including NT-proBNP risks only							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – including PND and NT-proBNP risks							
Patisiran	12.79	4.58	[redacted]	4.52	6.21	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	-	-	-	-

‡ *Undiscounted*

As shown in Table 1, the removal of the PND-related mortality HRs from the company's updated model leads to a lower modelled risk of death for patients in all health states, except for PND0-II, NT-proBNP<3,000pg/mL. In turn, this leads to a marked increase in the expected survival durations for patients in both the patisiran and BSC groups (see Figure 1). As shown in Table 2, removing the PND-related mortality HRs has a substantial impact on the model results:

- Mean survival for the BSC group is increased from 8.27 (original model) to 14.53 years (company's new model). This represents an increase of 6.27 years.
- The incremental QALYs gained for the patisiran group are increased – this is a consequence of the extended survival in the BSC group together with the company's assumptions of time-dependent HRQoL and the assumption that BSC-treated patients cannot transition to improved health states. The ERG notes that according to the company's model, per-cycle QALY gains in the BSC group become negative after 4 cycles (2 years) and remain negative for every subsequent cycle. The assumption of increased survival for these patients therefore increases the number of QALYs lost by patients receiving BSC.
- Mean costs for the BSC group are more than doubled (BSC costs including PND and NT-proBNP risks = [redacted]; BSC costs including NT-proBNP risks only = [redacted]). This is a consequence of extended survival for BSC and the assumption that BSC-treated patients cannot transition to improved health states. Under the company's new scenario, virtually all of the extended survival time for BSC patients is spent in PND IV (the worst and most expensive health state).
- When both PND and NT-proBNP mortality risks are included in the company's updated model, the ICER for patisiran versus BSC is [redacted] per QALY gained. When only NT-proBNP risks are applied, the ICER is reduced to £80,730 per QALY gained.

The ERG's critique of the evidence used to inform this aspect of the model and the methods used to derive HRs can be found in the ERG report (Section 5.3.3, critical appraisal point 5). The ERG agrees

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that there is uncertainty regarding the expected survival duration of patients with hATTR amyloidosis. However, the ERG has several concerns regarding the appropriateness of the company's new mortality assumptions.

- As described above, the company's new survival assumptions have a substantial impact upon the expected survival, QALYs, costs and cost-effectiveness estimates.
- According to the ECD, the Appraisal Committee previously accepted the company's original approach to modelling mortality risks. The ECD states: *"The clinical experts agreed with the company's approach of combining both the effect of polyneuropathy and cardiac involvement, and explained that patients usually die from cardiac complications. They noted that the hazard ratios for each PND/NT-proBNP combination were largely plausible. In its preferred analysis, the ERG assessed the impact of removing the mortality effect in patients with no cardiac involvement. The committee recognised the complexities of the company's approach and its limitations, but concluded that this approach was acceptable because of the lack of other evidence"* (NICE ECD,[1] Section 4.16).
- The company's original submission included details relating to the company's efforts to validate their original model (see CS,[4] Section 12.2.5, Table D11). The CS states that the clinicians that the company consulted: (i) agreed with the inclusion of mortality due to PND; (ii) agreed with the use of Suhr *et al*[3] (in the absence of other sources), and (iii) believed that the estimated survival gains for the BSC group were *"within the realm of plausibility."* Given that the estimated mean survival gains for the BSC group in the updated model have increased by 6.27 years compared with the original model, the ERG considers it unlikely that the company's clinical advisors would still believe that the company's modelled survival estimates remain plausible. However, the company's additional evidence submission does not provide any information regarding this, and the CS provided little information regarding the questions that the company asked the clinicians when attempting to validate the original model.
- In April 2019, inotersen received a positive recommendation from NICE.[5] The inotersen model used the PND-related HRs derived from the original patisiran model[4] (applied to states defined by FAP), but did not include additional mortality risks for patients with NT-proBNP NT-proBNP<3,000pg/mL.
- Additional information provided by the company in late April 2019 (page 7) suggests that the inclusion of NT-proBNP-related mortality only or using PND-related mortality only within the patisiran model produces similar survival estimates for BSC (14.53 years versus 11.05 years). The ERG disagrees with the company's view that these estimates are similar.
- The company's additional evidence submission highlights that the ERG presented an analysis in which PND-related mortality risks were removed (see ERG report, Table 34, exploratory scenario analysis 11). The ERG notes that this analysis was presented to highlight the

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significant impact of the assumption of time- and state-dependent improvements in HRQoL for patisiran and time- and state-dependent worsening in HRQoL for BSC on the ICER for patisiran.

- The ICER patisiran model[6] included mortality risks associated with increasing FAP stage and cardiac involvement.

The ERG believes that the company's updated mortality assumptions are inconsistent with the assumptions previously agreed by the Appraisal Committee, the company's clinical advisors, the NICE inotersen model[5] and the ICER patisiran model.[6] As such, the ERG does not consider the company's updated mortality assumptions to be reasonable. However, for the sake of consistency with the NICE inotersen appraisal, Section 3 presents additional ERG analyses in which only PND-related mortality risks are applied within the model (NT-proBNP risks are removed).

2.3 Additional GI-related disutilities applied to the BSC group

The company's updated model includes time- and state-dependent utilities based on a regression model fitted to EQ-5D data from APOLLO. Within the patisiran group, HRQoL in each state is assumed to increase at a constant rate for 5 years and subsequently plateau; within the BSC group, HRQoL is assumed decrease at a constant rate for 5 years and subsequently plateau. The ERG believes that the duration over which these increases/decreases in HRQoL in each state are applied has been accepted by the NICE Appraisal Committee. The company's updated model includes an additional assumption whereby patients with PND>I in the BSC group incur further time-independent GI-related disutilities, based on values taken from a UK catalogue of utility values for chronic conditions in the UK (Sullivan *et al*[7]). Patients in PND II are assumed to incur a disutility of -0.0727 during each model cycle (based on the reported disutility for "ICD-9 564 Funct Digestive Dis Nec"). Patients in PND IIIA to IV are assumed to incur a disutility of -0.1243 during each model cycle (based on the reported values for "ICD-9 564 Funct Digestive Dis Nec" plus "ICD-9 569 Oth Intestinal Disorders"). Amongst others, these ICD codes include some forms of constipation, irritable bowel syndrome, post-gastric surgery syndromes, vomiting and other disorders post-surgery, diarrhoea, megacolon, and neurogenic bowel.

The company's updated utility profiles for the BSC group are illustrated in Figure 2 (note – the utility values shown assume that no patient changes health state over time). The impact of these GI-related disutilities on the ICER for patisiran versus BSC are shown in Table 3. As shown in the table, the inclusion of these additional disutilities for BSC increases the magnitude of the QALY losses in the BSC group and reduces the ICER for patisiran versus BSC by around [redacted].

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Figure 2: Company's updated utilities for BSC group (excluding caregiver disutilities)

Table 3: Company's updated model results – with/without additional GI-related disutilities

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – time-dependent utilities capped at 5-years, with GI-related disutilities							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – time-dependent utilities capped at 5-years, no GI-related disutilities							
Patisiran	16.62	4.04	[redacted]	2.09	7.47	[redacted]	[redacted]
BSC	14.53	-3.43	[redacted]	-	-	-	-

‡ Undiscounted

The ERG has several concerns regarding the inclusion of these new GI-related disutilities:

- The ERG understands that the company's approach to modelling improvement (patisiran) or worsening (BSC) in EQ-5D within each PND health state over time is an attempt to reflect those aspects of hATTR amyloidosis which are not captured in the company's definition of the model health states (i.e. by PND or NT-proBNP). The extrapolation of EQ-5D over time within a health state is unconventional and the ERG believes that this approach leads to a lack of clarity regarding the actual health state that is being valued. The ERG also notes that if the company's inclusion of further GI-related disutilities in the updated model is intended to quantify other

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factors which are not reflected in the definition of PND- and NT-proBNP-related health states, this then means that it is unclear what the time-dependent utilities are intended to reflect. The ERG believes that the inclusion of both effects on HRQoL may represent double-counting and, as such, may overestimate the negative health impact of the disease on patients treated with BSC. This is an area of uncertainty and there are no data to support or refute this.

- The company's additional evidence submission[2] does not provide any information regarding whether the health states valued in Sullivan *et al*[7] reflect the specific health impacts which they consider are not captured in the existing time- and state-dependent utilities.
- The company's updated model applies the additional GI-related disutilities from Sullivan *et al*[7] to every BSC patient with PND>1 at all timepoints. This appears to imply that: (i) all BSC patients with PND>1 will experience these symptoms indefinitely, and that (ii) none of the impact of GI-related symptoms is reflected in the time- and state-dependent EQ-5D estimates. Given that hATTR amyloidosis is a progressive disease in which symptoms accumulate over time, this assumption is unlikely to be reasonable.
- The application of constant disutilities to all patients with PND>I together with the time- and state-dependent EQ-5D estimates is inconsistent with the predictions of the company's regression model fitted to EQ-5D data from APOLLO.
- The company's updated model does not apply the additional GI-related disutilities to those patients who have discontinued patisiran. This implies that even after discontinuation, patisiran provides a lifetime protective effect against GI-related autonomic dysfunction. The ERG believes that if it is appropriate to include these GI-related disutilities, they should be applied to all patients who are receiving BSC, irrespective of whether they have previously received patisiran.
- The amended version of the company's updated model includes GI-related disutilities for patisiran discontinuers, but includes an additional assumption that these GI-related symptoms do not manifest fully after discontinuation. The ERG notes that this assumption favours patisiran as it still assumes some degree of protective effect of the drug following discontinuation.

2.4 Discontinuation of patisiran

The company's updated model includes a stopping rule whereby patients discontinue patisiran upon progression to PND IV. The company has also re-implemented the time-to-treatment discontinuation function applied in the original model.[4] The company's updated analysis assumes that:

(i) Patients in any health state can discontinue patisiran, with per-cycle probabilities determined by the log normal time-to-treatment discontinuation function fitted to data from APOLLO

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(ii) Patients who reach PND IV will immediately discontinue patisiran and subsequently receive BSC

(iii) The prognosis of patients who have discontinued patisiran is governed by the BSC transition probabilities

(iv) HRQoL for patisiran discontinuers is assumed to decrease according to the slope of the time-dependent HRQoL functions for BSC, starting from the patient's last "on treatment" utility value. This is applied using a weighted average contribution of the fraction of the cohort already off-treatment in the previous cycle and of the cohort discontinuing in the current cycle.[2]

(v) In the company's updated model, patisiran discontinuers do not incur any the additional GI-related disutilities described in Section 2.3.

(vi) In the amended version of the company's updated model, patisiran discontinuers do not incur the full GI-related disutilities; instead, they incur 10% of the full GI-related disutilities. In addition, lower limits for utilities for patisiran discontinuers were calculated using complex formulae which attempt to estimate a weighted average between the cohort discontinuing in the current cycle and the cohort already off-treatment in the previous cycle.

The impact of the PND IV stopping rule and the re-introduction of the APOLLO time-to-treatment discontinuation function on the ICER for patisiran versus BSC is shown in Table 4.

Table 4: Company's updated model results – with/without discontinuation

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – time to treatment discontinuation curve and PND IV stopping rule							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model –PND IV stopping rule only							
Patisiran	16.74	4.33	[redacted]	2.21	9.00	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Company's new model – time to treatment discontinuation curve only							
Patisiran	17.94	6.95	[redacted]	3.41	11.45	[redacted]	[redacted]
BSC	14.53	-4.50	[redacted]	-	-	-	-

‡ Undiscounted

With respect to the inclusion of the stopping rule and time-to-treatment discontinuation curve from APOLLO, the ERG notes the following:

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- As described above, the ERG believes that if it is considered appropriate to apply the additional GI-related disutilities to the BSC group, these should also be applied to patients who have discontinued patisiran (at the point of discontinuation).
- The simultaneous application of the time-to-treatment discontinuation function from APOLLO and the company's PND IV stopping rule may overestimate the joint discontinuation risk.
- The company's approach for estimating HRQoL in patisiran discontinuers is problematic given the company's assumptions regarding time- and state-dependent utilities. The appropriate approach for implementing the company's intended assumptions regarding HRQoL (i.e. no rebound effect on HRQoL after discontinuation) would require the use of tunnel states which account for the subsequent HRQoL trajectory of patients in a given health state who discontinue patisiran at each timepoint in the model. This would require the use of tunnel states which explicitly account for changes in HRQoL for incident and prevalent discontinuers. This could be implemented using a semi-Markov or patient-level simulation approach; however, the ERG does not believe that it is possible to appropriately implement the company's intended assumptions using the company's existing Markov model structure.
- Following receipt of the updated model, the ERG asked the company to clarify the assumptions underpinning their implementation of post-discontinuation utility in the model. In response, the company stated that these were the same as those used in the NICE inotersen model. The ERG does not believe that this claim is accurate. The company's amended model includes complex formulae which attempt to approximate the appropriate approach described above. The ERG was unable to fully understand the logic underpinning the company's calculations.
- The impact of this structural issue cannot be fully assessed using the company's model structure.

2.5 Inclusion of caregiver disutilities

The company's updated model includes caregiver disutilities; these were taken from the Akcea model developed to inform the NICE appraisal of inotersen.[8] The impact of including these disutilities on the ICER for patisiran is shown in Table 5.

Table 5: Company's updated model results – with/without caregiver disutilities

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's new model – including caregiver disutilities from inotersen model							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-

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Company's new model – no caregiver disutilities							
Patisiran	16.62	4.31	[redacted]	2.09	7.14	[redacted]	[redacted]
BSC	14.53	-2.83	[redacted]	-	-	-	-

‡ *Undiscounted*

The NICE Final Evaluation Document (FED) for inotersen[5] states the "*The committee accepted the company's revised approach and concluded that it was appropriate to assume 1 carer in stages 1 and 2, and 2 carers in stage 3 of the model."* The ERG believes that for the sake of consistency, it is reasonable to include these additional caregiver disutilities in the patisiran model.

2.6 Use of inotersen time-to-treatment discontinuation function

The company's additional evidence submission highlights that discontinuation rates were higher for inotersen compared with patisiran and presents an analysis in which the time-to-treatment discontinuation function for inotersen is applied to the patisiran group. This reduces the ICER for patisiran. The ERG believes that it is inappropriate to use the inotersen time-to-treatment discontinuation function as this relates to a different technology. The ERG believes that these analyses should be disregarded.

3. Additional analyses undertaken by the ERG

The ERG has undertaken additional exploratory analyses using the amended version of the company's updated model. All of the ERG's exploratory analyses have the following features:

(i) GI-related disutility is applied equally to patients receiving BSC and to patients who have discontinued patisiran. This is applied outside of the minimum/maximum utility caps.

(ii) Carer disutilities are included in all analyses. These are applied outside of the minimum/maximum utility caps.

(iii) All analyses include the PND IV stopping rule and the APOLLO time-to-treatment discontinuation function.

(iv) All analyses include the current PAS for patisiran.

The following analyses were undertaken using this amended version of the model:

- Exploratory analysis 1. This analysis applies features (i) to (iv) within the company's updated base case model (NT-proBNP mortality only).
- Exploratory analysis 2a. This analysis applies features (i) to (iv) and includes both PND- and NT-proBNP-related mortality.
- Exploratory analysis 2b. This analysis is the same as 2a, with GI-related disutilities halved.
- Exploratory analysis 2c. This analysis is the same as 2a, with GI-related disutilities removed.

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- Exploratory analysis 3a. This analysis applies features (i) to (iv) and includes both PND-related mortality only.
- Exploratory analysis 3b. This analysis is the same as 3a, with GI-related disutilities halved.
- Exploratory analysis 3c. This analysis is the same as 3a, with GI-related disutilities removed.

The results of the analyses are presented in Table 6.

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Table 6: Additional analyses of the company's updated model undertaken by the ERG

Option	Absolute			Incremental			
	LYGs‡	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Company's updated model base case							
Patisiran	16.62	4.03	[redacted]	2.09	8.71	[redacted]	**£80,730**
BSC	14.53	-4.67	[redacted]	-	-	-	-
Exploratory analysis 1. Updated model, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	16.62	3.55	[redacted]	2.09	8.23	[redacted]	[redacted]
BSC	14.53	-4.67	[redacted]	-	-	-	-
Exploratory analysis 2a. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	12.79	4.37	[redacted]	4.52	6.00	[redacted]	[redacted]
BSC	8.27	-1.63	[redacted]	-	-	-	-
Exploratory analysis 2b. Updated model, PND and NT-proBNP mortality HRs, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	12.79	4.47	[redacted]	4.52	5.73	[redacted]	[redacted]
BSC	8.27	-1.25	[redacted]	-	-	-	-
Exploratory analysis 2c. Updated model, PND and NT-proBNP mortality HRs, no GI-related disutilities applied for discontinuers or BSC							
Patisiran	12.79	4.58	[redacted]	4.52	5.46	[redacted]	[redacted]
BSC	8.27	-0.88	[redacted]	-	-	-	-
Exploratory analysis 3a. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC							
Patisiran	14.25	4.09	[redacted]	3.21	7.09	[redacted]	[redacted]
BSC	11.05	-3.00	[redacted]	-	-	-	-
Exploratory analysis 3b. Updated model, PND mortality HRs only, GI-related disutilities applied immediately for discontinuers and BSC (all GI-related disutility halved)							
Patisiran	14.25	4.25	[redacted]	3.21	6.75	[redacted]	**£125,256**
BSC	11.05	-2.50	[redacted]	-	-	-	-
Exploratory analysis 3c. Updated model, PND mortality HRs only, no GI-related disutilities applied for discontinuers or BSC							
Patisiran	14.25	4.41	[redacted]	3.21	6.42	[redacted]	[redacted]
BSC	11.05	-2.01	[redacted]	-	-	-	-

As shown in Table 6, including PND-related mortality, with or without additional risks for patients with high NT-proBNP, leads to ICERs which are higher than those presented in the company's additional evidence submission. The ERG believes that some caution should be given to the interpretation of results generated using the company's model due to the method used to calculate post-discontinuation

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utilities. An exploratory “worst-case” scenario analysis conducted by the ERG, in which the utility profile for patisiran discontinuers was set equal to that for the BSC group, produced ICERs which were around [redacted] higher than those presented in Table 6. Whilst this aspect of the company’s model is incorrectly implemented due to its structural limitations, it may not have a large impact on the estimated ICER for patisiran.

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